Design and construction of oxa/aza heterocycles *via* addition-cyclization strategies

Final synopsis

OF THE Ph.D. THESIS TO BE SUBMITTED TO THE

MANGALORE UNIVERSITY

FOR THE AWARD OF THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

By

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(MU/EXB/PhD./CR.08/Chem/2022-23/E.25)

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FINAL SYNOPSIS OF THE THESIS TO BE SUBMITTED TO THE MANGALORE UNIVERSITY

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Title of the Thesis	**: Design and construction of oxa/aza heterocycles *via* addition-cyclization strategies**
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Thesis entitled **"Design and construction of oxa/aza heterocycles *via* addition-cyclization strategies"**

The Michael addition, a cornerstone reaction in organic chemistry, is widely utilized for constructing carbon-carbon bonds, particularly in the formation of complex molecular architectures. This reaction involves the nucleophilic addition of a Michael donor to an α,β-unsaturated carbonyl compound, known as the Michael acceptor. When followed by an intramolecular cyclization, this strategy becomes a powerful tool for synthesizing a diverse array of cyclic and polycyclic compounds, notably spiro compounds[1].

Among the numerous Michael acceptors available, *para*-quinone methides[2] (*p*-QMs) arylidene pyrazolones[3] and isoxazolones[4] stand out for their exceptional reactivity and versatility in forming spirocyclic systems. *p*-QMs are highly reactive intermediates featuring a methylene group adjacent to a quinone moiety. Their ability to undergo rapid nucleophilic addition makes them ideal candidates for Michael addition reactions. Upon addition of a nucleophile, subsequent cyclization can efficiently generate spiro compounds, offering a pathway to structurally complex and biologically relevant molecules.

On the other hand, arylidene pyrazolones and isoxazolones, serve as another effective class of Michael acceptors. Due to their widespread occurrence in numerous medicines and physiologically active substances, these skeletons constitute significant structural components. These intermediates also facilitate the formation of spirocyclic structures through Michael addition followed by *ipso*-cyclization. Michael addition and *ipso*-cyclization serve as a great pathway for synthesizing a variety of spiro-molecules using different nucleophilic partners.

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Spiro compounds have been reported to possess a wide range of biological activities, including antimicrobial, anticancer, anti-inflammatory, and antiviral properties[5].

Inspired by the above concepts, we have developed new methods for the synthesis of new spiro and cyclized molecules. We herein present our studies directed towards developing new methodologies under transition metal-free conditions employing Michael addition and *ipso*-cyclization strategies. These explorations have been divided into 4 CHAPTERS as shown below.

CHAPTER 1: 1,6-Additions and oxidative annulations of sulfonylphthalides and *para*-quinone methides

In this chapter we have demonstrated the KO^{t}Bu-mediated addition of sulfonylphthalides to *p*-quinone methides. These addition reactions led to the selective synthesis of isochroman-1,4-diones (Table 1A) and addition products[6] (Table 1B). Interestingly, isochroman-1,4-diones were obtained *via* an unprecedented oxidative annulation pathway. This work highlights a wide variety of substrates, good yields, shorter reaction times and ambient reaction conditions. All the products obtained were characterized and confirmed by spectroscopic analysis and single crystal XRD analysis.

Table 1A: *Oxidative annulation of sulfonylphthalides with p-quinone methides*

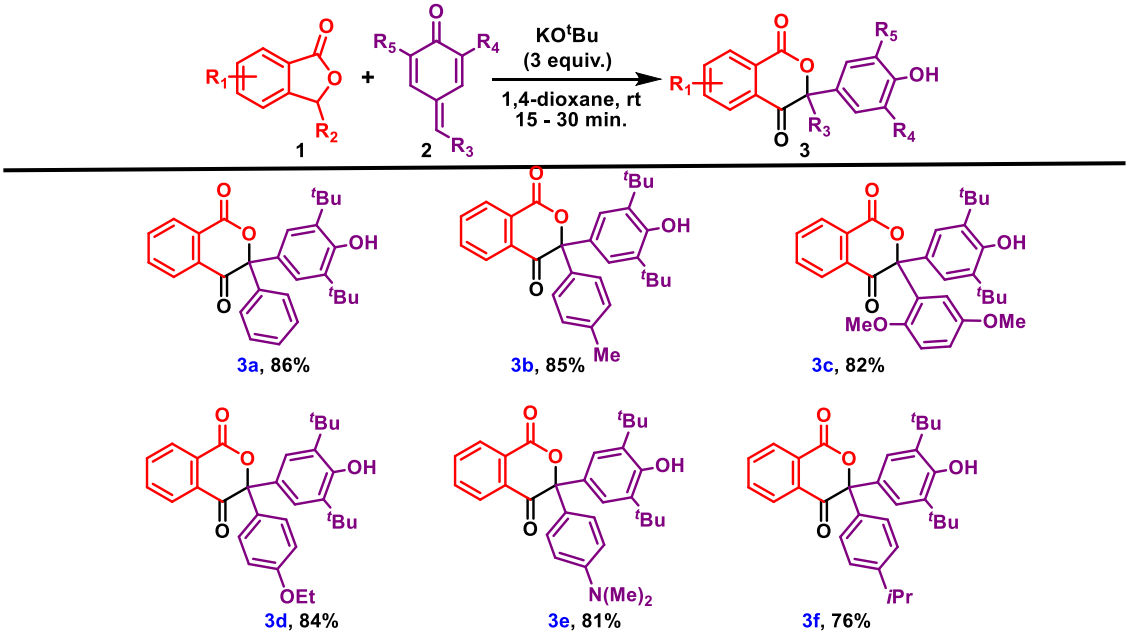

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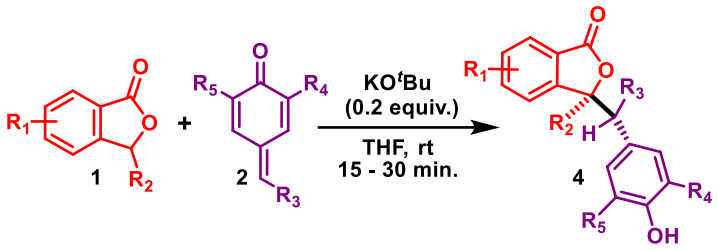
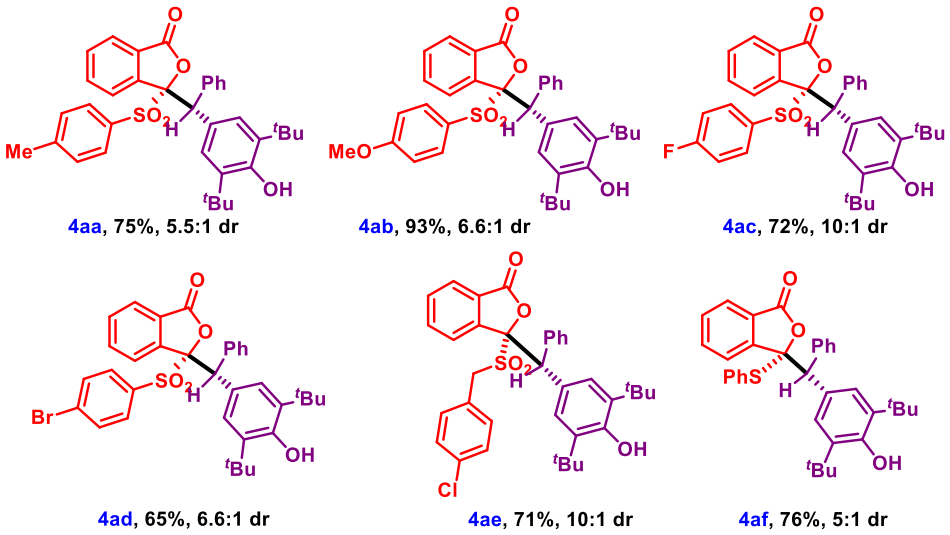
Table 1B: *1,6-Addition of sulfonylphthalides to p-quinone methides*



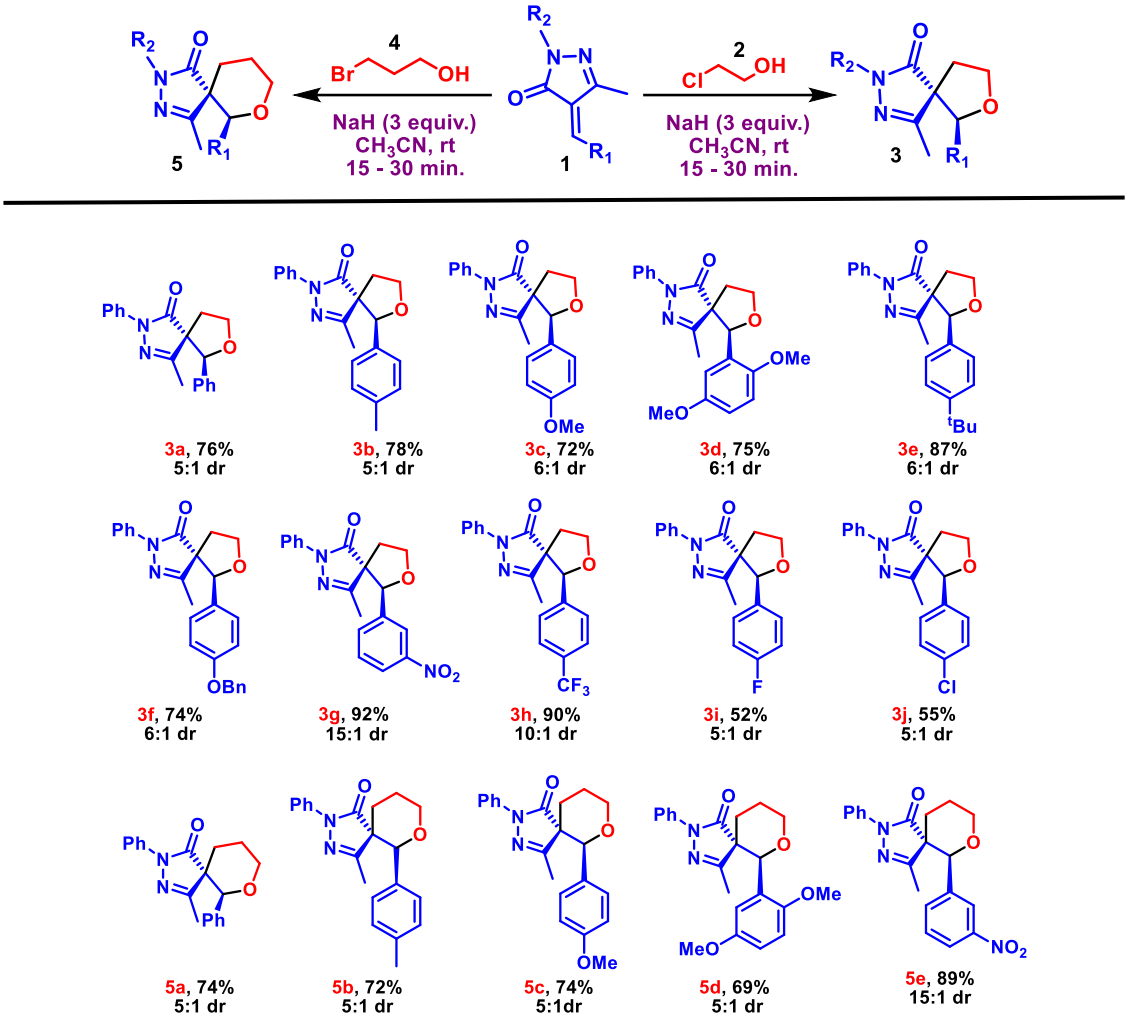


CHAPTER 2: Synthesis of spiro-pyrazolones-tetrahydrofurans/pyrans *via ipso*-cyclization

In this chapter, synthesis of spiro-pyrazolones-tetrahydrofurans and pyrans[7] using unsaturated pyrazolones and haloalcohols via a base-mediated cascade addition followed by *ipso*-cyclization is described. Some of the representative examples are shown in Table 2. Noteworthy aspects of this methodology include shorter reaction time, expansive substrate applicability, very good yields and mild reaction conditions without the need for transition metals. Synthesized products were characterized and confirmed by spectroscopic analysis and single-crystal XRD analysis.

7 K. K. Gond and M. R. Maddani, *New J. Chem.,* **2024**, 48, 8671.

Table 2: *Synthesis of spiro-pyrazolone-tetrahydrofurans/pyrans*



CHAPTER 3: Synthesis of spiro-pyrazolone-pyrrolidinones *via ipso*-cyclization

This chapter discloses the convenient synthesis of spiro-pyrazolone-pyrrolidinones *via* NaH mediated cascade addition, *ipso*-cyclization of unsaturated pyrazolones with 2-chloro-*N*-phenylacetamides[8]. This method offers an efficient route to a variety of highly functionalized spiro-pyrazolone-pyrrolidinones with good yields under transition metal-free conditions (Table 3). All the synthesized products are characterized and confirmed by spectroscopic analysis and single crystal XRD analysis.

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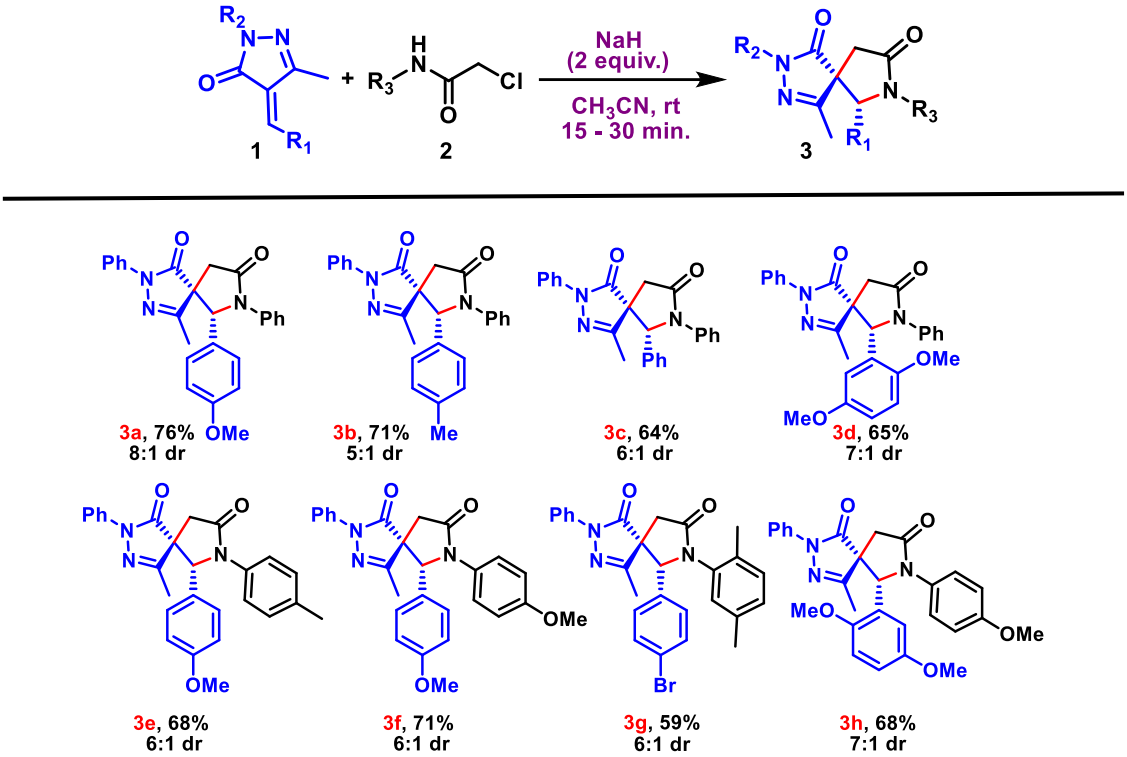
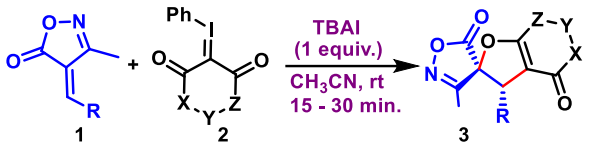
Table 3: *Synthesis of spiro-pyrazolone-pyrrolidinones*

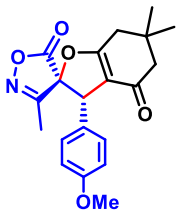


CHAPTER 4: Iodide mediated synthesis spiro-benzofuran-isoxazolediones

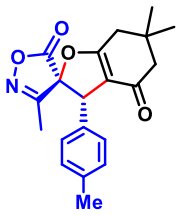
Encouraged by the previous results on the synthesis of spiro compounds using isoxazolones, we further extended strategy using iodonium ylide and arylidene isoxazolones. In this Chapter, an efficient synthesis of spirobenzofuran isoxazolediones mediated by an additive TBAI is described. This method offers an efficient route to a variety of functionalized spiro-benzofuran-isoxazolediones with good yields. Some of the representative examples are shown in Table 4. All the synthesized products have been characterized and confirmed by spectroscopic analysis. Also, one of the products obtained was further confirmed by single crystal XRD analysis.

Table 4: *Synthesis spiro-benzofuran-isoxazolediones*

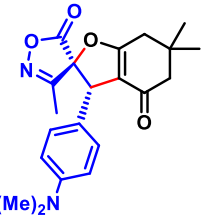




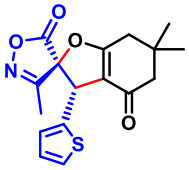
3a, 89%, 8:1 dr



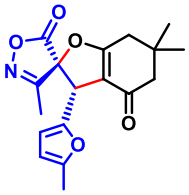
3b, 90%, 8:1 dr



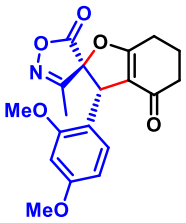
3c, 65%, 5:1 dr



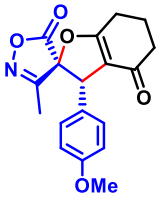
3d, 76%, 5:1 dr



3e, 67%, 5:1 dr



3f, 56%, 5:1 dr



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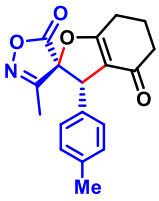
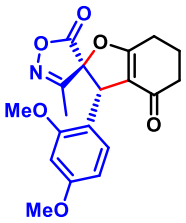


3h, 90%, 6:1 dr



3i, 56%, 5:1 dr